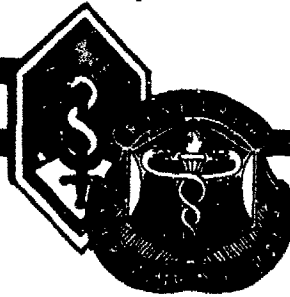AD-A258 012

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Effects of Terfenadine and Diphenhydramine on Brain Activity and Performance in a UH-60 Flight Simulator

By

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Biomedical Applications Research Division

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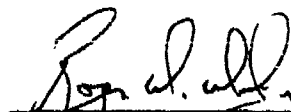
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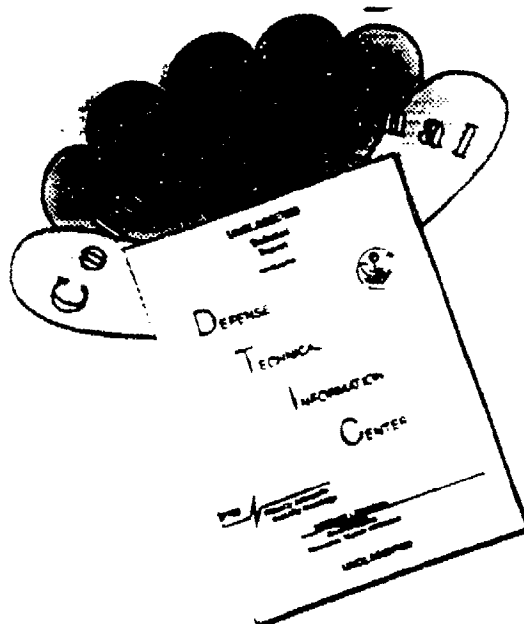 Research Division

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The effects of terfenadine, diphenhydramine, and a placebo on flight performance, resting electroencephalographic (EEG) activity, and auditory and visual evoked potental tasks were investigated. Twelve male Army aviators served as subjects in a double-blind, repeated measures experimental design. The results indicated that neither diphenhydramine nor terfenadine effected flight performance. Regarding resting EEG, diphenhydramine caused a decrease of alpha power at all electrode sites. For all sites with the exception of Cz, diphenhydramine also caused a decrease of power in the beta band. The P300 component of the auditory evoked potential was unaffected by either of the drugs. The amplitude of the visual P300 was suppressed under diphenhydramine relative to placebo while the latency was unaffected. The results of this study highlight the importance of measuring multiple aspects of performance in assessing the impact of a drug. While flight performance was unaffected by either drug, the indications from measures of brain activity are that terfenadine is much less sedating. Therefore, it is a more attractive alternative (Continued)

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Introduction

U.S. Army personnel face the potential threat of operating under the stressful environment of a chemically-contaminated battlefield. Not only will the stresses of battle impinge upon their performance, the use of chemical defense antidote and pretreatment therapies likely will interact with such stresses. Since the effects of stress-inducing variables on performance frequently require timely and accurate assessment, proven standardized testing methodologies are highly desirable.

Standardization and validation of assessment methodologies is required to achieve the goal of maintaining a body of results which is consistent from laboratory to laboratory and from drug to drug. As a means of addressing this need, the U.S. Army Aeromedical Research Laboratory (USAARL), Fort Rucker, AL, has developed a multidisciplinary performance assessment strategy which includes the collection of electrophysiological and cognitive measures on aviators in conjunction with measures of simulated flight performance. All of these measures show promise for use in assessing and predicting decrements in military aviator performance which result from chemical defense antidote and pretreatment drugs. While development of this methodology is ongoing, an evaluation program was implemented.

In order to assess the sensitivity and stability of our performance assessment methodology, we proposed a comparison of diphenhydramine (an antihistamine with known sedative effects) to terfenadine (an antihistamine which acts without sedative effects). Results of this investigation also provided information to flight surgeons about the performance effects of terfenadine and diphenhydramine on the performance of U.S. Army aviators. Once the sensitivity and stability of this assessment strategy were established, it could be used to evaluate the effects of drugs for which military doctrine would suggest possible future use.

H_1-receptor antagonists (antihistamines)

The H_1-receptor antagonists, often referred to as the antihistamines, were introduced into clinical practice over 40 years ago, and since then they have been used extensively in allergic conditions. In addition to their H_1-antagonist properties, these agents frequently have antagonist actions at other receptors. In particular, a number have anticholinergic properties and are used clinically to treat such conditions as motion sickness and vertigo.

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Most antihistamines have similar pharmacological actions and therapeutic applications and are usually associated with impaired central nervous system (CNS) function as indicated by drowsiness and altered psychomotor performance. Therefore, the use of antihistamines by aircrews has, heretofore, been limited because of their sedative side effects. All the classical antihistamines readily cross the blood-brain barrier and enter the CNS and are usually associated with CNS-related side effects. Central depression usually accompanies therapeutic doses of these drugs, and the potential for a variety of effects exists as a sequel to their use. Primary among these are sedative effects indicated by drowsiness, lassitude, and fatigue. Not all individuals suffer such effects to the same degree; however, all the classical antihistamines are capable of producing these effects, and claims of nonsedation made for some of these drugs have proved unwarranted. Stimulation of the CNS can also occur and is occasionally encountered in individuals given conventional doses of classical antihistamines, resulting in restlessness, nervousness, and inability to sleep. In some situations, sedation and other CNS depressant effects may be clinically useful. However, in many instances, these effects interfere with an individual's ability to perform normal activities.

Pharmacology

Antihistamines (H_1-receptor antagonists) competitively inhibit most of the pharmacologic actions of histamine. Histamine produces its effects through actions at two types of receptors, the H_1- and the H_2-receptors. Depending on the receptors with which they interact, antagonists of histamine are currently classified as H_1- or H_2-antagonists (or blockers). The term antihistamine has historically been used to describe drugs that act as H_1-receptor antagonists. Although drugs that antagonize H_2-receptors are available, these drugs generally are not referred to as antihistamines, but rather as H_2-receptor antagonists.

Antihistamines appear to act by blocking H_1-receptor sites, thereby preventing the action of histamine on the cell. They do not chemically inactivate or physiologically antagonize histamine, nor do they prevent the release of histamine. Their characteristic pharmacological activity is largely predictable from knowing the responses that involve interaction of histamine with H_1-receptors. All of the available antagonists are reversible, competitive inhibitors of the actions of histamine. In addition, a number of these drugs have anticholinergic properties and tend to inhibit responses to acetylcholine that

are mediated by muscarinic receptors, and therefore, manifest these anti-muscarinic or atropine-like actions during clinical usage.

The H_1-blockers can both stimulate and depress the CNS. How the various H_1-blocking drugs produce their depressant and stimulant effects is uncertain. The drugs bind with high affinity to H_1-receptors in the brain, and the effects may reflect antagonism of this binding action. Other, perhaps unrelated, central actions include the ability of certain H_1-blockers to counter motion sickness and vertigo.

The drowsiness associated with the use of antihistamines has been attributed to various mechanisms such as the inhibition of histamine-N-methyltransferase and the blockade of central histaminergic receptors. Other mechanisms, including serotonergic antagonism, anticholinergic activity, and blockade of central α-adrenoceptors, may also be factors. Although these various mechanisms have been proposed, it appears that sedative effects are dependent on the ability of a particular drug to cross the blood-brain barrier and gain access to the CNS. A common property of many antihistamines is the ease with which they cross the blood-brain barrier. In contrast, terfenadine crosses the blood-brain barrier with great difficulty and appears to be associated with little, if any, impaired CNS function.

Diphenhydramine and terfenadine

Diphenhydramine hydrochloride is an antihistamine with anticholinergic and sedative effects. A single oral dose is quickly absorbed with maximum activity occurring in approximately 1 hour. The duration of activity following an average dose (25 to 50 mg) is from 4 to 6 hours. It is widely distributed throughout the body, including the CNS. Little, if any, is excreted unchanged in the urine; most appears as the degradation products of metabolic transformation in the liver which are almost completely excreted within 24 hours.

Distribution of diphenhydramine hydrochloride has not been fully characterized, but it apparently undergoes first-pass metabolism in the liver and only about 40-50 percent of the oral dose reaches systemic circulation as unchanged diphenhydramine. Carruthers et al. (1978) reported that the terminal half-life for diphenhydramine ranged from 2.4 to 3.9 hours in their sample. The drug is approximately 82 percent bound to plasma proteins in vitro. Plasma concentrations appear to decline in a monophasic manner, although some pharmacokinetics data suggest a polyphasic elimination (Carruthers et al., 1978). Diphenhydramine is considered characteristic of the antihistamines with peripheral

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and sedative effects. Therefore, it was chosen as a classic active control that could be expected to yield the behavioral decrements needed for validity assessment.

Unacceptable decrements in performance may not be an inevitable sequel of antihistamine use. Terfenadine, unlike other currently available antihistamines, does not appear to appreciably distribute into the CNS at usual dosages. The introduction of terfenadine as a new selective H_1-receptor antagonist has aroused considerable interest because of its reported freedom from sedative side effects. Terfenadine is chemically and pharmacologically distinct from other antihistamines because it appears to be a peripherally specific histamine H_1-receptor antagonist. Terfenadine possesses no anticholinergic, antiserotonergic, antiadrenergic, nor anti-H_2-histaminic properties and has been demonstrated to be free of CNS side effects in pharmacological, toxicological, and clinical studies.

Animal studies (Cheng et al., 1977; Cheng and Woodward, 1982a; 1982b) have demonstrated it to be a peripherally specific histamine H_1-receptor antagonist with no observed sedative or anticholinergic effects at effective antihistaminic doses. Studies indicate that at such doses neither terfenadine nor its metabolites penetrate the blood-brain barrier well (Rose et al., 1982; Wiech and Martin, 1982).

An oral dose is well absorbed from the gastrointestinal tract and is rapidly and extensively biotransformed. Following administration of a single 60 mg tablet, detectable plasma levels were observed within 0.5 hour. Plasma levels peaked at about 2 hours after administration. A distribution half-life of 3.4 hours was followed by an elimination half-life of 20.25 hours. The effective half-life has been estimated to be 12 hours. Terfenadine is extensively (97 percent) bound to human serum protein. Elimination studies showed that fecal excretion accounted for 60 percent of the dose while 40 percent of the dose was eliminated via the urine (Merrell Dow Pharmaceuticals, Inc., 1988).

Electrophysiological measures

It has been recognized that the sedative properties of antihistamines influence the human electroencephalogram (EEG), and much work has been done on the EEG correlates of fluctuations in wakefulness as well as drug-induced EEG changes (Fink and Irwin, 1979; Goldstein, Murphree, and Pfeiffer, 1968; Vollmer et al., 1983). Under resting conditions it has been found that alpha activity (8.0 to 12.5 Hz) is generally increased while slow

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activity (delta, 0.5 to 4.5 Hz and theta, 4.5 to 8.0 Hz) is generally decreased. In contrast, sedation is generally characterized by a slowing and a decrease of alpha activity and an increase in delta and theta activity (Vollmer et al., 1983).

A number of studies have been conducted investigating these effects. Goldstein, Murphree, and Pfeiffer (1968) conducted a comparative study of EEG effects of antihistamines in normal volunteers. Their study resulted in the classification of distinct categories of antihistamines. EEG recordings were obtained prior to the administration of the drug, 1 hour postdrug, and every hour thereafter for a 6-hour period. Diphenhydramine and promethazine were categorized as low-energy sedatives wherein frequency analysis revealed an increase in the low-frequency bands (delta and theta 1 to 6 Hz), a decrease in the alpha band (8 to 12 Hz), and a small increase in the higher-frequency range (beta, 18 to 36 Hz). In effect, the EEG pattern reflected predominantly low amplitude, therefore labeled "low energy," sedation. Another category defined during this investigation included "high-energy" sedation (with chlorpheniramine and phenindamine) where there were increases in the low- and high-frequency bands but little change in the alpha range. Their final category was "no change" (with diphenylpyraline and azatadine) in which global energy analyses revealed no significant departure from the control baseline.

Fink and Irwin (1979) investigated CNS effects of the antihistamines. They found that terfenadine failed to elicit the characteristic EEG or behavioral effects of sedative antihistamines, and was distinguishable from diphenhydramine. They recorded EEGs before the administration of the drug, then hourly for the next 4 hours. In their study, terfenadine was indistinguishable from placebo in the first 2 hours after oral administration, and the difference was questionable thereafter. However, diphenhydramine was distinguished from both placebo and terfenadine because it increased EEG slow wave activity (i.e., delta, 1 to 5 Hz) and decreased power in the theta-alpha range (6 to 13 Hz).

Although assessments of spontaneous EEG activity have been used to show the effects of terfenadine and diphenhydramine upon generalized activation levels (Fink and Irwin, 1979; 1981), apparently no one has examined the effects of these drugs on cortical evoked responses. Given the performance effects of diphenhydramine and the reliance upon CNS depression as an explanatory mechanism, the inclusion of evoked response tests provides useful information for explaining significant findings.

More specifically, the inclusion of P300 tasks (in addition to spontaneous EEGs) offers insight into drug-induced performance problems resulting from stimulus evaluation difficulties or

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central processing decrements. In either case, a drug which impairs the input or the processing of information will no doubt affect performance if the information is task relevant and the increased response time from input to output is significant.

The evoked responses obtained from a task in which subjects are required to attend to the occurrence of an infrequently presented stimulus consist of several components which offer information of interest. The earliest of these components (occurring within 250 ms of stimulus presentation) are generally considered to be influenced by the physical parameters of the stimulus (Pritchard, 1981). Therefore, any factor which either changes the stimulus properties directly (altering the actual stimulus) or indirectly (altering the subject's perception of the stimulus) will influence some dimension (amplitude, latency, or both) of at least one of the early components of the evoked response.

The late components of the response fall into a different category. Specifically, the P300 wave (a positive-going component occurring from approximately 250 to 450 ms) is thought to be largely dissociated from the physical parameters of the eliciting stimulus (Sutton et al., 1965). Rather, the wave is thought to index decision-related processes (Brandeis and Lehmann, 1986). The actual relationship among input parameters, processing demands, and evoked response components is, however, not as simple as it may at first appear. There are studies which suggest an independence of P300 from "stimulus input" changes (Towle, Sutcliffe, and Sokol, 1985; Sokol, 1986), and those which indicate a more complex situation (Fagan, Westgate, and Yolton, 1986; Papanicolaou et al., 1985). Yet, it can be said that P300 provides an indication of the amount of cognitive processing required to successfully evaluate task-relevant events under a variety of conditions, regardless of the precise mechanisms involved.

' Taken together with more generalized assessments of global CNS activation (spontaneous EEG) and tests of cognitive performance, evoked response data served as a useful adjunct to substantiating the degrading or enhancing effects of a pharmacological substance. Furthermore, to eliminate the possibility of modality-specific effects on sensory mechanisms confounding the interpretation of performance or electrophysiological effects of diphenhydramine and terfenadine, P300s were obtained via both visual and auditory modalities.

Driving performance

While few studies have investigated the effects of antihistamines on flight performance (Neves-Pinto, Lima, and Teixeira, 1989), several investigators have examined antihistamines' effects on driving performance. Betts et al. (1984) reported on the driving performance of experienced women drivers after ingestion of the centrally-active antihistamine, triprolidine, and terfenadine. They found triprolidine greatly impaired driving behavior, whereas terfenadine did not.

O'Hanlon (1988) discussed the development of an instrumented automobile which provides data on the amount of weaving a subject exhibits while performing an actual driving task on a 100 km highway circuit. He and his co-workers developed a dependent measure called the "weaving index" which is basically an RMS error score of the subject's ability to maintain the vehicle within the lane boundaries. O'Hanlon and others (Riedel, Schoenmakers, and O'Hanlon, 1987 cited in O'Hanlon, 1988) then used this measure to assess the effects of terfenadine (60 mg), loratadine (10 mg), and triprolidine (10 mg) on actual driving performance. Terfenadine and loratadine had no effect on the weaving index, while triprolidine produced impairment of driving ability equivalent to that observed in previous research with blood alcohol concentrations of 0.05 percent (Louwerens et al., 1987 cited in O'Hanlon, 1988).

Method

Subjects

Twelve male, volunteer U.S. Army aviators, qualified as UH-60 pilots, were used as participants. They were between the ages of 23 and 46 (mean of 32.4), and possessed normal or correct-to-normal vision. Subjects completed a thorough physical examination, including questions pertaining to their history of caffeine and alcohol consumption, prior to acceptance in the study.

Subjects were required to refrain from the use of alcoholic and caffeinated beverages and any other medications for the duration of the study, and urine was collected once each morning for a caffeine assay. Saliva litmus tests were used for alcohol screening.

Apparatus

Flight performance

Flight performance assessments were conducted using the USAARL UH-60 flight simulator system which includes an operational crew station, computer-generated visual display, six-degree motion system, specially constructed environmental conditioning equipment, and a complete data acquisition system. The visual display and motion system presented a standard, daytime flight environment. The environmental conditioning system was used to maintain a constant cockpit temperature of 72 degrees F and a constant cockpit humidity of 70 percent.

Flight data were acquired on a VAX 11/780 interfaced to a Perkin-Elmer digital computer which controlled the UH-60 flight simulator. This system is capable of monitoring any aspect of simulator control, from heading, air speed, and altitude, to Doppler readouts, switch positions, or operator console inputs. For the purposes of this investigation, only 13 channels of data were monitored continuously, and these are listed in Table 1, Appendix A.

The acquired data points were stored on the VAX 11/780 until the conclusion of the study, and then were transferred to the main USAARL computer, a VAX 11/785. Once data were available for all 12 subjects, flight performance scores including root mean square (RMS) errors were derived using specialized software routines developed in the Laboratory (Jones and Higdon, 1991).

Electroencephalography

A Cadwell Spectrum 32 brain mapper was used to collect and analyze the electrophysiological data. Evoked potential protocols included both auditory and visual P300 tasks. EEG data were collected on 21 monopolar (mastoid referenced) leads and analyzed with regard to measures of absolute and power among delta, theta, alpha, and beta bands. Also, an indication of the symmetry of activity and the phase coherence among a variety of channels was calculated. Evoked potential data were scored with regard to measures of latency (ms) and amplitude (microvolts) of the N75, P100, N145, and P300 components. The stored analyses of both EEG and evoked response data were transferred to the VAX for statistical analyses.

Procedure

Subjects participated for a period of 2 weeks, and a staggered schedule allowed testing of two aviators concurrently. Each aviator was given four, 1.5-hour practice sessions on the simulator during the first week (Monday through Thursday). On Friday, the actual drug testing began. Subjects were exposed to one drug condition (terfenadine, diphenhydramine, placebo) on each of 3 drug-administration days (Table 2, Appendix A). The first drug test occurred on Friday of the training week, the second test occurred on Monday of the following week, and the third test occurred on Thursday. There were 2 control days between drug-administration days to provide time for one drug to clear the body before the next drug was given. Drug administration was counterbalanced and double-blind.

To maintain the double-blind dose administration procedure, an equal number of pills was given to each subject at each dose time. Since terfenadine and diphenhydramine have different half-lives, placebo pills were administered when applicable. Subjects received four doses under each drug condition: one on the evening preceding testing, one on the morning of each test day, and two subsequent doses 4 and 8 hours later.

During terfenadine administration, subjects were given 120 mg active terfenadine and placebo diphenhydramine at their initial dose (the night preceding testing). At the morning dose, subjects were given 60 mg terfenadine and placebo diphenhydramine. At the subsequent dose times, these subjects were given placebo terfenadine and placebo diphenhydramine.

During diphenhydramine administration, subjects were given placebo diphenhydramine and placebo terfenadine at the initial dose time (on the evening preceding testing). At the morning dose time on the test day, subjects were given 100 mg of diphenhydramine and placebo terfenadine. At the subsequent dose times, immediately prior to the simulator flight and 4 hours later, they were given 50 mg diphenhydramine and placebo terfenadine.

During the placebo administration, subjects were given placebo diphenhydramine and placebo terfenadine at each of the dose times. Placebo pills were identical in appearance to the active drug. On drug testing days, subjects were required to report to USAARL at 0530 to receive the morning dose. Following the dose, the subjects ate breakfast and prepared for the upcoming test.

The flight performance evaluation required the subjects to perform the maneuvers listed in Table 3, Appendix A. In

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addition, subjects performed a set of emergency procedures between the ILS approach and the second takeoff.

The same sequence of maneuvers was used for every subject during each of the training flights and testing flights. These maneuvers are of the type typically flown in a UH-60 aircraft. They are fully described in the Aircrew Training Manual (Department of the Army, 1988).

The entire profile lasted approximately 1.5 hours while performance was measured using the simulator's computerized performance monitoring system which was described earlier. During each flight, a safety pilot was present to ensure the proper sequencing of all flight maneuvers. In addition, the safety pilot marked the beginning and ending point of each individual maneuver for the purpose of delimiting subsequent computer scoring. There were two safety pilots who performed this function, and both were marking individual maneuvers according to predetermined criteria in order to exclude transitional periods. Thus, the safety pilots would inform the subject about the maneuver to be flown, and he would mark the start point of the maneuver only when the subject had reasonably stabilized the simulator into the proper configuration for that maneuver.

Following the flight profile, subjects performed a battery of cognitive tasks which have been described elsewhere (Verona and Stephens, 1991). After a short break, subjects were prepared for electrophysiological data collection. EEGs were collected from a 21 monopolar (mastoid referenced) lead montage with collodion-affixed electrodes in accordance with the International 10-20 System to accommodate brain mapping with the Cadwell Spectrum 32. This permitted an assessment of the overall extent of cortical activation under terfenadine and diphenhydramine. The amplifier settings for the Cadwell Spectrum 32 Brain Mapper were constant at a sensitivity of 5.0, high filter at 70 Hz, and low filter at 0.53 Hz. The 60 Hz notch filter was used. Data were collected in a dimly lit, sound attenuated test booth 2 hours and 50 minutes postdrug administration. Each session consisted of eyes-opened followed by eyes-closed (60 seconds each), after which multiple channel analyses were performed on relatively artifact-free, 2.5-second epochs.

The auditory P300 task consisted of a series of 200 tones presented simultaneously to both ears. The rare stimulus was a 70 dB, 2000 Hz tone with a rise time, a plateau, and a fall time of 10 ms, a cosine envelope, and a fixed phase with no masking noise. The common stimulus was identical with the exception of the frequency, which was 500 Hz. The rare tone was randomly presented 40 times among the 160 common tones. The presentation rate was 1 stimulus per second. During this task, EEG was

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sampled from all standard 10-20 leads with the additions of Fpz and Oz. The reference point was A1 linked to A2. The high filter was set at 100 Hz and the low filter was set at 1 Hz.

The visual P300 task consisted of a series of 200 check patterns presented via a television monitor located approximately 1.5 meters from the subject's face. The common stimulus was an 8 x 8 check pattern and the rare stimulus was a 64 x 64 check pattern. The full field width of the 15-inch monitor was used, and there was a small fixation point located in the middle of the screen. The rare check pattern was randomly presented 40 times among the 160 common stimuli, and the stimulation frequency remained constant at 1 Hz. Meanwhile, EEG was sampled from the same 21 leads, with the same reference point as described above for the auditory P300.

Results

General

The flight performance data were divided into a specific series of maneuvers, and the various control parameters (heading, altitude, etc.) were scored using locally developed computerized routines. The scoring consisted of calculating RMS errors for each parameter from each maneuver, and storing these RMS errors in data files which were subjected to statistical analyses.

The parameters selected for scoring changed depending upon the maneuver under consideration. Obviously, it made no sense to score heading deviations during turns or altitude deviations during climbs and descents. Thus, only the meaningful parameters were used, and these are listed in Table 4, Appendix A.

In order to calculate RMS errors for each of these parameters, an ideal value was selected against which the actual control accuracy was evaluated. For instance, if a straight-and-level segment was supposed to be flown at a heading of 180 degrees, an altitude of 1000 feet, and an airspeed of 90 knots, RMS errors were calculated by determining the actual control deviations around each of these values for each of the parameters (heading, altitude, and airspeed). In this study, the ideal values were either specified directly, or they were determined via computer algorithm as outlined below.

For some of the maneuvers, a computerized algorithm was used in which a dynamic ideal value was selected from the first sample of data (on heading, altitude, and airspeed only) which occurred after the safety pilot marked the start point of each maneuver.

However, if the first sample did not deviate more that a set amount from the values shown in Table 3, Appendix A, the actual table value was used. For a dynamic value to have been selected, the control deviation on heading had to exceed 10 degrees of the table value, the deviation on altitude had to exceed 100 feet, and the airspeed value had to exceed 10 knots. If this occurred, the dynamic value used for RMS error calculation was rounded to either the nearest 10 degrees (for heading), 10 knots (for airspeed), or the nearest 100 feet (for altitude). This dynamic value was then used as the ideal standard for the specific parameter throughout the entire maneuver. If no dynamic value was required, the table value was used to score the entire maneuver.

In addition to the use of dynamic ideal values, one other aspect of the scoring procedure deserves mention. Because of the possibility that the safety pilots may have inadvertently marked the start point of a maneuver before the subject had stabilized the simulator, or marked the stop point of a maneuver after a subject had begun a transition, the data were scored in two ways. The first method involved calculating RMS errors from the actual start point to the actual stop point of each maneuver as indicated by the safety pilot marks. The second method involved calculating RMS errors from 5 seconds after the actual start point of a maneuver to 5 seconds prior to the actual stop point of the maneuver. The first set of analyses was conducted using only the first (untrimmed) scoring method, but a second set of analyses, for some maneuvers, was conducted using the second (trimmed) method. It was felt that particular maneuvers such as turns might benefit from the trimming procedure, and in fact, there were differences between the results of untrimmed versus trimmed scoring methods. However, in this report, only the trimmed data are reported for the two types of standard rate turns, the s-turns, the climbs, and the descents.

Flight data analyses

Data from all 12 subjects under each of the 3 drug conditions were analyzed with a series of repeated measures analyses of variance (ANOVAs) using BMDP4V. Prior to the ANOVAs, 1 drug day (diphenhydramine) for subject 7 and 1 drug day (placebo) for subject 8 were estimated using BMDPAM in which the cell means for all other available data were substituted for the missing data. Following the data estimation, RMS errors were transformed into log naturals in order to reduce the impact of occasional extremely large error values. After data transformation, a series of ANOVAs was conducted--some of which were one-way (with drug as the factor) and some of which were

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two-way (drug x maneuver iteration). The average elapsed time-from-dose for each maneuver is presented in Table 5, Appendix A.

Acceleration

There were three acceleration maneuvers completed by each subject during each drug testing day. These were analyzed together in a two-way ANOVA. Results indicated that there were no differences in heading, altitude, slip, or roll control as a function of dose. Examination of mean transformed RMS errors shows clearly the lack of a significant effect--for example, the heading means were diphenhydramine=0.37, placebo=0.32, and terfenadine=0.38.

Climb

There were three climbs which were analyzed together. Once again, the two-way ANOVA did not indicate significant effects of the drugs on any aspect of flight performance. Heading, airspeed, slip, roll, and rate-of-climb all remained unchanged across the three conditions. For example, examination of the mean transformed RMS values for airspeed revealed: diphenhydramine=1.11, placebo=0.90, and terfenadine=1.05.

Descent

There were three descents analyzed in the same two-way ANOVA. This analysis indicated no drug main effects, but there was one drug x iteration interaction and two maneuver-iteration main effects. The drug x iteration interaction was observed on the slip measure $(F(2.40,26.39)=3.56, p=.036)$, and subsequent analysis of simple effects indicated a difference among the three drug conditions at only the first iteration of this maneuver $(F(1.77,19.51)=5.04, p=.02)$. Contrasts showed this effect was attributable to greater control error under diphenhydramine (mean=0.35) than under placebo (mean=0.24), but less control error under diphenhydramine than under terfenadine (mean=0.396). See Table 6, Appendix A. Given the absence of similar effects on the remaining maneuvers, it is unlikely that these differences are attributable to the effects of the drugs per se.

The first of the iteration main effects was observed on the airspeed measure $(F(2,22)=6.31, p=.007)$, where it could be seen that there was more control error on the first iteration of this maneuver (mean=1.094) than on the second (mean=0.846) or the third (mean=0.796). Contrasts for these effects are presented in Table 6, Appendix A.

The second iteration effect was observed on the rate-of-climb measure ($F(1.26,13.91)=7.68$, $p=.011$). Here, there was also more error during the first iteration of this maneuver (mean=4.553) than during the second (mean=4.299) or third (mean=4.109). Contrasts may be found in Table 6, Appendix A.

Deceleration

There was only one deceleration maneuver in the flight profile, and the ANOVA for it indicated there were no significant effects attributable to the drug conditions on heading, altitude, slip, or roll.

Instrument approach

There was also only one instrument approach in the profile. This maneuver occurred at about 42 minutes postdose, and because of its location at peak dose concentration and its sensitivity to stressors in the past, significant effects were expected. However, the ANOVA indicated no drug-related impact on airspeed control or on either localizer or glide slope tracking. The absence of any difference is clearly depicted in the mean localizer tracking errors where diphenhydramine=2.17, placebo=2.16, and terfenadine=2.13.

Left standard-rate turn

There were three of these standard-rate turns in the profile. There were no significant interactions and no differences among the three drug conditions. The analysis did indicate a difference among the three on rate-of-turn errors ($F(2,22)=4.87$, $p=0.018$) and slip errors ($F(1.42,15.59)=3.95$, $p=0.053$). With regard to rate-of-turn, the first (mean=0.231) and third (mean=0.218) iterations were better than the second (mean=0.276). With regard to slip, performance on the first iteration (mean=0.222) was better than the second (mean=0.298) or third (mean=0.301). Contrasts are listed in Table 7, Appendix A.

Right standard-rate turn

The six right turns were analyzed in a two-way ANOVA which revealed no drug main effects, but one drug x iteration interaction, and two iteration main effects. The drug x iteration interaction was found on the airspeed measure ($F(5.42,59.67)=2.42$, $p=0.042$). Subsequent analysis of simple effects indicated there was a difference among maneuver iterations under only diphenhydramine ($F(3.22,35.47)=2.96$,

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p=0.042). Contrasts showed this was attributable to better airspeed control during the fourth iteration (mean=0.872) than during the second (mean=1.303), fifth (mean=1.171), or sixth (mean=1.279) iterations (see Table 8, Appendix A). Once again, reasons for such a difference are not obvious at this point, but it is interesting to note that the fourth right turn was about 34 minutes postdose. Possibly the slight sedation produced by diphenhydramine prevented subjects from making frequent, small airspeed adjustments which might have increased the overall RMS error on the other turns.

The first maneuver-iteration effect was found on the rate-of-turn measure (F(2.99,32.89)=28.97, p<.001). The second iteration (mean=0.340) was worse than the first (mean=0.149), third (mean=0.180), fourth (mean=0.155), fifth (mean=0.162), and sixth (mean=0.191). Also, the first iteration was better than the sixth (see Table 8, Appendix A). The fact that the second turn was worse than all the others probably is due its short duration. Because the second turn was only 30 seconds long, subjects probably had difficulty fully stabilizing the aircraft into the maneuver before it was time to roll out.

The second iteration main effect was found on the slip measure (F(2.92,32.17)=8.33, p<.001). Here, it could be seen that the second iteration (mean=0.458) was worse than the first (mean=0.385), third (mean=0.401), fourth (mean=0.365), and sixth (mean=0.361)--findings consistent with those for the rate-of-turn measure. However, on slip, it was additionally found that fifth iteration (mean=0.470) was worse than the first, third, fourth, and sixth (See Table 8, Appendix A). The reasons for this reduced performance on the fifth iteration are unclear at this point.

S-turn

There was a single s-turn included in the flight profile. Analyses indicated this maneuver was unaffected by the drug conditions.

Straight-and-level

There were seven straight-and-level segments in each flight, and these were analyzed together in a two-way ANOVA. Results indicated no drug-related effects on any of the measures examined; however, there were maneuver-iteration differences with regard to heading (F(3.53,38.86)=3.03, p=0.034), airspeed (F(3.61,39.72)=3.40, p=0.020), slip (F(3.80,41.78)=5.83, p=0.001), and roll (F(3.14,34.56)=5.65, p=0.003). The contrasts for these effects are presented in Table 9, Appendix A.

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On the heading measure, the first iteration (mean=-0.305) was better than the second (mean=0.031), third (mean=0.014), fourth (mean=0.095), and seventh (mean=0.124). Also, the sixth (mean=-0.205) was better than the third, fourth, and seventh, and the fifth (mean=-0.148) was better than the seventh. This is quite similar to findings on the slip measure, where the first iteration (mean=-1.395) was better than the second (mean=-1.051), the third (mean=-1.105), and the seventh (mean=-0.857). In addition, the second iteration was worse than both the fifth (mean=-1.400) and seventh; the fourth (mean=-1.111) was worse than the fifth; and the fourth was better than the seventh. Finally, the fifth was also better than the seventh.

On both the airspeed measure and the roll measure, the first iteration of straight-and-level (SL) was better than any of the rest. For airspeed, the means were: SL1=-0.197, SL2=0.376, SL3=0.228, SL4=0.188, SL5=0.220, SL6=0.291, and SL7=0.294. For roll, the means were: SL1=-0.682, SL2=-0.182, SL3=-0.201, SL4=-0.162, SL5=-0.270, SL6=-0.168, and SL7=0.050.

Takeoff

There were two takeoffs included in each flight profile, and these were analyzed together. Results indicated there were no significant interactions or main effects on measures of heading control, slip control, or roll control during this maneuver.

Electrophysiology: Resting EEG

For purposes of statistical analyses, only the absolute power of delta (1.5-3.0 Hz), theta (3.0-8.0 Hz), alpha (8.0-13.0 Hz), and beta (13.0-20.0 Hz) from Fz, Cz, Pz, and Oz were examined. These data were analyzed with a series of two-way repeated measures analyses of variance with drug (diphenhydramine, placebo, and terfenadine) and eyes (opened, closed) as within-subjects factors. Missing data due to equipment failures and occasional excessive artifact were estimated by BMDPAM using the mean for those variables.

Frontal EEG activity

Analysis of the absolute power of activity evidenced by each of the major EEG bands at Fz revealed a number of effects; however, there were no significant interactions. Alpha activity was affected by the drug ($F(2,22)=4.36$, $p=.0253$) as was beta activity ($F(2,22)=4.36$, $p=.0253$). As shown in Figures 1 and 2, Appendix B, both the alpha and beta bands evidenced less activity

under diphenhydramine than under either placebo or terfenadine. See contrasts in Table 10, Appendix A. Also, there was an increase in activity for the following bands at eyes-closed compared to eyes-opened: theta - $(F(1,11)=9.25, p=.0112)$, alpha - $(F(1,11)=9.01, p=.0121)$, and beta - $(F(1,11)=17.57, p=.0015)$. See Table 11, Appendix A.

Central EEG activity

Central alpha activity revealed an interaction between drug and eyes $(F(2,22)=4.11, p=.0303)$, a main effect for drug $(F(2,22)=5.32, p=.0131)$, and a main effect on the eyes factor $(F(1,11)=12.12, p=.0051)$. There were also significant main effects on the eyes factor in the theta band $(F(1,11)=7.46, p=.0195)$ and the beta band $(F(1,11)=7.21, p=.0212)$. As seen in Figure 3, Appendix B, the drug x eyes interaction in the alpha band resulted from a drug effect at eyes-closed $(F(2,22)=6.95, p=.0046)$. Contrasts revealed the effect at eyes-closed was due to more alpha activity at placebo and terfenadine when compared to diphenhydramine (see Table 12, Appendix A). An example of this interaction is clearly depicted in the topographical brain maps shown in Figure 4, Appendix B.

The drug main effect (shown in Figure 5, Appendix B) occurred only in the alpha band where there was greater alpha activity for both placebo and terfenadine in comparison to diphenhydramine (see Table 13, Appendix A). This finding essentially supports the drug x eyes interaction discussed above.

The effects on the eyes factor for all three bands, theta, alpha, and beta, were due to an increase at eyes-closed in comparison to eyes-opened (see Table 14, Appendix A).

Parietal EEG activity

Analysis of the parietal lead revealed a drug main effect for the alpha band $(F(2,22)=6.71, p=.0053)$ and beta band $(F(2,22)=6.87, p=.0048)$ which can be seen in Figures 6 and 7, Appendix B. Contrasts revealed that the effects for both bands were due to greater amounts of activity under placebo and terfenadine as compared to diphenhydramine (see Table 15, Appendix A).

There were also significant effects in the eyes factor for theta $(F(1,11)=10.34, p=.0082)$, alpha $(F(1,11)=15.56, p=.0023)$, and beta $(F(1,11)=23.75, p=.0005)$. For all three bands, this effect again was due to increased activity at eyes-closed in comparison to eyes-opened (see Table 16, Appendix A).

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Occipital EEG activity

Analysis of the occipital lead revealed a drug main effect in the alpha band ($F(2,22)=4.37$, $p=.0252$) and the beta band ($F(2,22)=3.53$, $p=.0470$). See Figures 8 and 9, Appendix B. The effect for the alpha band was caused by reduced activity for diphenhydramine when compared to placebo and terfenadine. For the beta band, the decrease occurred when diphenhydramine was compared to terfenadine only (see Table 17, Appendix A).

There were also eyes main effects for theta ($F(1,11)=4.89$, $p=.0491$), alpha ($F(1,11)=13.41$, $p=.0037$), and beta ($F(1,11)=18.15$, $p=.0013$). These were due to an increase in activity at eyes-closed as compared to eyes-opened for all three bands (see Table 18, Appendix A).

Generally, there was a decrease in alpha and beta activity at all leads under the influence of diphenhydramine with the exception of Cz where the decrease was found only in alpha activity. There were no significant differences between placebo and terfenadine at any of the leads. Also, there were no significant two-way interactions at any of the leads except Cz where drug effects were found to vary as a function of whether eyes were opened or closed. At this lead there was a significant decrease in alpha activity under diphenhydramine at eyes-closed. With regard to main effects on the eyes (opened/closed) factor, there was an increase in theta, alpha, and beta activity at all leads under the eyes-closed condition when compared to the eyes-opened condition, as would have been expected.

Electrophysiology: Evoked potentials

For evoked potential data, analyses were performed for only midline electrode sites Cz and Pz. Latency and amplitude (scored from P300 to the preceding negative peak) of the P300 component of both auditory and visual evoked potentials were evaluated for each subject under each of the drug conditions. These data were submitted to a series of repeated measures analyses of variance with drug as the factor (diphenhydramine, placebo, and terfenadine). Missing data due to equipment failure for one subject's terfenadine day were estimated by substituting the group mean for terfenadine days. In addition, one subject's data from the frontal electrode site on his diphenhydramine day were unscoreable and were estimated by substituting the mean.

Auditory evoked potential

Results of the analyses for the latency and amplitude of the P300 at Cz and Pz revealed no significant effects.

Visual evoked potential

Results of analyses of visual P300 latency at Cz and Pz revealed no significant effects. Results of analysis of P300 amplitude at Cz revealed a significant drug effect $(F(1.98,21.77)=4.29, p=.0272)$ which resulted from a reduction of amplitude under diphenhydramine relative to placebo $(p=.0041)$. See Figure 10, Appendix B. Analysis of P300 amplitude at Pz also revealed a significant drug effect $(F(1.84,20.29)=3.64, p=.0479)$ due to a reduction in amplitude under diphenhydramine relative to placebo $(p=.0046)$. See Figure 10, Appendix B.

Discussion

These findings have implications for the determination of both the relative safety of taking these two antihistamines in an aviation environment and the sensitivity of the various assessment tools employed. Unexpectedly, neither diphenhydramine nor terfenadine affected flight performance. Other investigators (Neves-Pinto, Lima, and Teixeira, 1989) examining the influence of an antihistamine on simulator flight performance have also reported no effect due to the drug. However, the drug investigated was loratadine, a nonsedating antihistamine, and no sedating antihistamine condition was included as a control. Thus, the sensitivity of their simulated flight profile to a sedating drug was not demonstrated.

The subjects in this study, as a group, were sedated by diphenhydramine as indicated by the subjective measures of sleepiness and fatigue (Verona and Stephens, 1991). The most sensitive objective measures for detecting this effect were the electrophysiological ones. The aspects of flight performance measured in this study were unaffected by diphenhydramine.

One possible explanation for this lack of effect on flight performance is that the degree of degradation resulting from 50 mg of diphenhydramine was not sufficient to produce a dramatic increase in simulator control error for the group as a whole. In addition, individual differences in response to antihistamines have been documented previously. In one study (Carruthers et al., 1978), 50 mg of diphenhydramine produced sleep in approximately half of the subjects during the first hour after injection. Variation in response to the drug between individuals

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in our study may have contributed to the lack of drug effect for the group.

An alternative explanation lies in the fact that the total flight profile was broken down into a series of maneuvers. Each of these maneuvers was analyzed separately for RMS error on relevant parameters. Thus, the components of flight performance assessed in this investigation primarily tested psychomotor tracking. In the UH-60, the psychomotor tracking aspects of flight performance are facilitated by the automated flight control system. Consequently, the lack of effect of diphenhydramine could have resulted from subjects compensating for the degrading effects of diphenhydramine through reliance on this automated system.

The results of this study regarding resting EEG corroborated the research previously summarized by Fink and Irwin (1979), Goldstein, Murphree, and Pfeiffer (1968), and Vollmer et al. (1983). All of these studies substantiated the effects of sedation as being a decrease in alpha activity and an increase in slow wave activity. Vollmer et al. (1983) also revealed a small increase in the beta range following administration of a sedating antihistamine as did Fink and Irwin (1979).

While this study did not reveal any significant effects for slow wave activity, there were significant effects for all sites under the alpha and beta bands. In all cases, diphenhydramine caused a decrease of alpha power. For all sites with the exception of Cz, diphenhydramine caused a decrease in the beta band. This is in contradiction to the small increase in beta that Vollmer et al. (1983) and Fink and Irwin (1979) found. Such a discrepancy may have occurred because of differences in the band widths for the higher frequency range. The beta band width for the Vollmer et al. (1983) study was 18 to 36 Hz whereas the band width for this study was 13 to 20 Hz. The beta band for the Fink and Irwin (1979) study likewise included frequencies above 20 Hz.

With regard to the comparison of diphenhydramine, placebo, and terfenadine, this study confirmed the findings of Fink and Irwin (1979). They concluded that terfenadine does not affect EEG characteristics and is very similar to placebo.

This study also examined the difference in EEG spectral components under eyes-opened and eyes-closed conditions. In the studies by Fink and Irwin (1979); Goldstein, Murphree, and Pfeiffer (1968); and Vollmer et al. (1983), EEGs were collected under resting conditions. Only one author stated that all subjects' eyes were closed, but it is assumed that the other investigators also recorded in an eyes-closed state. As discussed in the results section of this report, only Cz revealed

a significant interaction between drug and the eyes factor. In the eyes-closed condition, placebo and terfenadine increased alpha activity while diphenhydramine resulted in a decrease in alpha activity. However, there were no differences in EEG activity as a function of drug in the eyes-opened condition. Thus, the sedative impact of some antihistamines appears to be masked in the eyes-opened, resting EEG even though it is pronounced when eyes are closed.

The results from the visual P300 data support the conclusion that diphenhydramine is creating generalized sedation as was evident from the EEG. The amplitude of the visual P300 was suppressed under diphenhydramine relative to placebo, but the latency was unaffected. This discrepancy suggests the level of sedation produced by diphenhydramine in this study was not substantial enough to produce gross decrements in cognitive processes. Such a conclusion is consistent with the findings that flight performance was unimpaired.

The lack of an effect on the auditory P300 lends support to earlier findings of Swire et al. (1989) in their evaluation of the sedating antihistamine, triprolidine. Those authors failed to detect either latency or amplitude changes in the auditory P300 despite the fact that subjects subjectively felt impaired and there was evidence of performance decrements.

The present investigation was apparently the first to employ both a visual and an auditory P300 in the assessment of antihistamine effects. As reported, there were inconsistencies in the findings between the two tasks.

One possible explanation for this discrepancy could be that diphenhydramine significantly affected the initial stimulus registration in the visual task, but not in the auditory task, to the extent that subsequent target stimulus evaluation was degraded. McMenemy, Tharion, and Rauch (1989) found that diphenhydramine did increase the latency of early components of the visual evoked response, and they cited evidence this may have been due to visual disturbances. However, it is unlikely that any visual impairment, if present in our subjects, would have obscured the target stimulus to the point where processing was impaired. It is generally accepted that P300 is largely independent of physical parameters of the eliciting stimulus (Sutton et al., 1965), and some investigators have reported that P300 is even immune to the effects of extensive visual blur (Sokol, 1986). In the present study, we used a 15-inch, 8 x 8 check pattern for the common visual stimulus and a 15-inch, 64 x 64 check pattern for the target--such a difference would have been difficult to obscure.

A second possible explanation for differences between the results of the visual and auditory P300 tasks centers around differences in task demands. In the visual P300, subjects were presented with simple (large) check patterns which reversed every second and which were occasionally interspersed with a more complex (small) check pattern--the target. It is possible that the requirement to evaluate such a complex visual scenario is more demanding than the requirement to differentiate a 2000 Hz tone from a 500 Hz tone (the stimuli used in the auditory P300). Thus, if there were only small drug effects, as suggested by the lack of decrements in the performance data, it is reasonable to hypothesize that these effects would tend to impair only the more demanding of the two P300 tasks. Swire et al. (1989) did offer "low task demands" as one possible explanation for their failure to detect auditory P300 changes from a drug which produced sedation. However, they favored an explanation in which H_1 receptors are not involved in the generation of the auditory P300 citing the work of Pineda, Foote, and Neville (1986) who suggest that the auditory P300 is generated by the activity of noradrenergic neurons in the locus coeruleus.

The results of this study highlight the importance of measuring multiple aspects of performance in assessing the impact of a drug. While flight performance was unaffected by either drug, the indications from measures of brain activity are that terfenadine is much less sedating. Therefore, it is a more attractive alternative for the treatment of allergic symptoms in the aviator population or in any population where compromised performance is potentially dangerous.

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Appendix A

Tables

Table 1.

Flight performance measures

Channel	Variable	Units	Rate
1	Magnetic heading	Degrees	5 Hz
2	Indicated altitude	Feet	5 Hz
3	Indicated airspeed	Knots	5 Hz
4	Indicated rate of climb	Feet per min	5 Hz
5	Rate of turn	Degrees per s	5 Hz
6	Roll angle	Degrees	5 Hz
7	Indicated slip	N-D	5 Hz
8	Radar altitude	Feet	5 Hz
9	Aircraft Y position	N-D	5 Hz
10	Aircraft X position	N-D	5 Hz
11	Aircraft Z position	Feet	5 Hz
12	Localizer needle	Dots	5 Hz
13	Glideslope needle	Dots	5 Hz

Table 2.

Drug dosage schedule

		Subject Schedule 1	Subject Schedule 2
Week 1			
Thursday	1730	Dose/Drug 1	
	1830		Dose/Drug 1
Friday	0530	Dose/Drug 1	
	0630		Dose/Drug 1
	.		
	.	.	
	.		
	0930	Dose/Drug 1	
	1030		Dose/Drug 1
	.		
	.		
	.		
	1330	Dose/Drug 1	
	1430		Dose/Drug 1
Week 2			
Sunday	1730	Dose/Drug 2	
	1830		Dose/Drug 2
Monday	0530	Dose/Drug 2	
	0630		Dose/Drug 2
	.		
	.		
	.		
	0930	Dose/Drug 2	
	1030		Dose/Drug 2
	.		
	.		
	.		
	1330	Dose/Drug 2	
	1430		Dose/Drug 2
Wednesday	1730	Dose/Drug 3	
	1830		Dose/Drug 3

Table 2. (continued)

Drug dosage schedule

		Subject Schedule 1	Subject Schedule 2
Week 2			
Thursday	0530	Dose/Drug 3	
	0630		Dose/Drug 3
	.		
	.		
	.		
	0930	Dose/Drug 3	
	1030		Dose/Drug 3
	.		
	.		
	.		
	1330	Dose/Drug 3	
	1430		Dose/Drug 3

Table 3.

Flight profile

Est.Start	Duration	Maneuver	Hdg	Alt	AS	To	From	Description
00:00	120	TAKEOFF	060	----	---	2000	0	Takeoff from IC #2 to 80 KIAS
02:00	90	ACC	060	2000	---	120	80	Accelerate to 120 KIAS
03:30	90	LSRT	---	2000	120	150	60	Left turn 270 deg to 150 deg
05:00	120	CLIMB	150	----	120	3000	2000	To 3000 ft 500 fpm from 2000 ft
07:00	90	SL	150	3000	120	---	---	3000 ft, 150 deg, 120 KIAS
08:30	150	RSRT	---	3000	120	240	150	Right turn 450 deg
11:00	60	ACC	240	3000	---	140	120	Accelerate to 140 KIAS
12:00	90	STURN	---	3000	140	240	240	S-Turn
13:30	60	CLIMB	240	----	140	3500	3000	To 3500 ft 500 fpm from 3000 ft
14:30	120	LSRT	---	3500	140	240	240	360 deg
16:30	60	SL	240	3500	140	---	---	3500 ft
17:30	60	DESC	240	----	140	3000	3500	To 3000 ft 500 fpm from 3500 ft
18:30	60	CLIMB	240	----	140	3500	3000	To 3500 ft 500 fpm from 3000 ft
19:30	30	RSRT	---	3500	140	330	240	90 deg
20:00	30	DEC	330	3500	---	120	140	Decelerate to 120 KIAS
20:30	60	DESC	330	----	120	3000	3500	To 3000 ft 500 fpm from 3500 ft
21:30	60	RSRT	---	3000	120	150	330	180 deg
22:30	60	SL	150	3000	120	---	---	3000 ft
23:30	60	RSRT	---	3000	120	330	150	180 deg
24:30	60	SL	330	3000	120	---	---	3000 ft
25:30	60	DESC	330	----	120	2500	3000	To 2500 ft 500 fpm from 3000 ft
26:30	240	ILS	060	----	120	---	---	ILS
30:30	120	TAKEOFF	060	----	---	2000	0	Takeoff from IC #2 to 80 KIAS
32:30	90	ACC	060	2000	---	120	80	Accelerate to 120 KIAS
34:00	30	LSRT	---	2000	120	330	60	Left turn 90 deg to 330 deg
34:30	60	SL	330	2000	120	---	---	2000 ft
35:30	60	RSRT	---	2000	120	150	330	180 deg
36:30	60	SL	150	2000	120	---	---	2000 ft
37:30	60	RSRT	---	2000	120	330	150	180 deg
38:30	60	SL	330	2000	120	---	---	2000 ft

Table 4.

Parameters scored for each maneuver

Maneuver	Parameter
Acceleration	Heading, altitude, slip, roll
Climb	Heading, airspeed, slip, roll, rate of climb
Deceleration	Heading, altitude, slip, roll
Descent	Heading, airspeed, slip, roll, rate of climb
ILS	Airspeed, localizer, glideslope
L. Std Rt Turn	Rate of turn, altitude, airspeed, slip, roll
R. Std Rt Turn	Rate of turn, altitude, airspeed, slip, roll
Straight & Level	Heading, altitude, airspeed, slip, roll
S-Turn	Altitude, airspeed, slip
Takeoff	Heading, slip, roll

Table 5.

Averaged elapsed time from dose

Maneuver	Avg elapsed time from dose	Max time from dose	Min time from dose
Takeoff	0: 5:58	0:13:24	0: 3: 6
Acceleration	0: 7:33	0:19:24	0: 4:29
Left std rt tn	0: 9:11	0:21: 8	0: 6: 7
Climb	0:10:50	0:22:54	0: 7:35
Straight & lev	0:13: 2	0:25: 5	0: 9:57
Right std rt tn	0:14:40	0:26:45	0:11:33
Acceleration	0:17:17	0:29:24	0:14:10
S-turn	0:18:41	0:30:40	0:15:16
Climb	0:20:11	0:31:58	0:16:36
Left st rt tn	0:21:27	0:33:15	0:17:36
Straight & lev	0:24:10	0:35:41	0:20: 7
Descent	0:25:27	0:36:58	0:21:20
Climb	0:26:41	0:38:17	0:22:30
Right std rt tn	0:27:58	0:39:26	0:23:33
Deceleration	0:28:56	0:40:21	0:24:10
Descent	0:29:50	0:41:26	0:24:48
Right std rt tn	0:31:22	0:42:42	0:26:48
Straight & lev	0:32:31	0:43:57	0:28: 1
Right std rt tn	0:33:48	0:45: 1	0:29: 8
Straight & lev	0:35: 1	0:46:12	0:30:15
Descent	0:36:13	0:47:23	0:31:32
Instrument lndg	0:42:52	0:52:50	0:35: 9
Takeoff	0:56:51	1: 7: 1	0:46:11
Acceleration	0:58:20	1: 8:30	0:47:41
Left std rt tn	0:59:58	1:10: 5	0:49:17
Straight & lev	1: 0:38	1:10:39	0:50: 2
Right std rt tn	1: 1:45	1:11:53	0:51: 8
Straight & lev	1: 2:56	1:12:58	0:52:16
Right std rt tn	1: 4: 5	1:14:30	0:53:26
Straight & lev	1: 5:11	1:15:18	0:54:33

Table 6.

Contrasts for descent iteration main effects (on airspeed and rate of climb) and drug x iteration interaction (on slip) at the first iteration

Iteration main effect					
Airspeed			Rate of climb		
Contrast	F	p	Contrast	F	p
1-2	13.97	0.003	1-2	12.55	0.005
1-3	8.52	0.014	1-3	8.93	0.012
2-3	ns		2-3	ns	

Drug x iteration interaction		
Slip		
Contrast	F	p
D-P	7.26	0.021
P-T	8.57	0.014
D-T	ns	

Table 7.

Contrasts for left standard-rate turn iteration main effects (on rate of turn and slip)

Iteration main effect					
Rate of turn			Slip		
Contrast	F	p	Contrast	F	p
1-2	6.49	0.027	1-2	15.12	0.002
1-3	ns		1-3	5.18	0.044
2-3	7.26	0.021	2-3	ns	

Table 8.

Contrasts for right standard-rate turn iteration main effects (on rate of turn, slip, and airspeed) and drug x iteration interaction (on airspeed) at diphenhydramine

Iteration main effect

	Rate of turn			Slip	
Contrast	F	p	Contrast	F	p
1-2	189.22	0.000	1-2	12.82	0.004
1-3	ns		1-3	ns	
1-4	ns		1-4	ns	
1-5	ns		1-5	23.50	0.000
1-6	5 25	0.043	1-6	ns	
2-3	47.48	0.000	2-3	7.59	0.019
2-4	130.74	0.000	2-4	16.05	0.002
2-5	87.64	0.000	2-5	ns	
2-6	39.60	0.000	2-6	11.67	0.006
3-4	ns		3-4	ns	
3-5	ns		3-5	7.73	0.018
3-6	ns		3-6	ns	
4-5	ns		4-5	17.03	0.002
4-6	ns		4-6	ns	
5-6	5.88	0.034	5-6	96.42	0.000

Drug x iteration interaction at diphenhydramine

	Airspeed	
Contrast	F	p
1-2	ns	
1-3	ns	
1-4	ns	
1-5	ns	
1-6	ns	
2-3	ns	
2-4	17.46	0.002
2-5	ns	
2-6	ns	
3-4	ns	
3-5	ns	
3-6	ns	
4-5	18.07	0.001
4-6	9.49	0.010
5-6	ns	

Table 9.

Contrasts for straight and level iteration main effects

	Iteration main effect				
Heading			**Airspeed**		
Contrast	F	p	Contrast	F	p
1-2	9.51	0.010	1-2	10.85	0.007
1-3	5.12	0.045	1-3	8.00	0.016
1-4	6.28	0.029	1-4	9.66	0.010
1-5	ns		1-5	11.36	0.006
1-6	ns		1-6	13.88	0.003
1-7	7.73	0.018	1-7	22.62	0.001
2-3	ns		2-3	ns	
2-4	ns		2-4	ns	
2-5	ns		2-5	ns	
2-6	ns		2-6	ns	
2-7	ns		2-7	ns	
3-4	ns		3-4	ns	
3-5	ns		3-5	ns	
3-6	5.14	0.045	3-6	ns	
3-7	ns		3-7	ns	
4-5	ns		4-5	ns	
4-6	4.80	0.051	4-6	ns	
4-7	ns		4-7	ns	
5-6	ns		5-6	ns	
5-7	5.62	0.037	5-7	ns	
6-7	10.01	0.009	6-7	ns	

Slip			**Roll**		
Contrast	F	p	Contrast	F	p
1-2	17.55	0.002	1-2	50.75	0.000
1-3	5.84	0.034	1-3	21.57	0.001
1-4	9.12	0.012	1-4	14.62	0.003
1-5	ns		1-5	17.21	0.002
1-6	ns		1-6	10.91	0.007
1-7	27.18	0.000	1-7	40.67	0.000
2-3	ns		2-3	ns	
2-4	ns		2-4	ns	
2-5	11.93	0.005	2-5	ns	
2-6	ns		2-6	ns	
2-7	5.33	0.041	2-7	ns	
3-4	ns		3-4	ns	
3-5	10.36	0.008	3-5	ns	
3-6	ns		3-6	ns	
3-7	5.25	0.043	3-7	ns	
4-5	5.08	0.046	4-5	ns	
4-6	ns		4-6	ns	

Table 9. (continued)

Contrasts for straight and level iteration main effects

	Slip				Roll	
Contrast	F	p	Contrast	F	p	
4-7	5.16	0.044	4-7	ns		
5-6	ns		5-6	ns		
5-7	37.58	0.000	5-7	11.64	0.006	
6-7	12.93	0.004	6-7	ns		

Table 10.

Contrasts for drug effect for EEG: Fz, alpha and beta

	Contrast	F	p
	Diphenhydramine - Placebo	5.11	.0451
Alpha	Diphenhydramine - Terfenadine	11.20	.0065
	Placebo - Terfenadine		ns
	Diphenhydramine - Placebo	5.65	.0367
Beta	Diphenhydramine - Terfenadine	9.24	.0112
	Placebo - Terfenadine		ns

Table 11.

Mean absolute power for EEG: Fz

	Eyes-opened	Eyes-closed
Theta	18.14	24.72
Alpha	17.95	25.37
Beta	4.65	6.31

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Table 12.

Contrasts for drug x eyes interaction for EEG: Cz, alpha

	Contrast	F	p
Drug at	Diphenhydramine - Placebo	7.30	.0206
eyes	Diphenhydramine - Terfenadine	15.48	.0023
closed	Placebo - Terfenadine	ns	

Table 13.

Contrasts for drug effect for EEG: Cz, alpha

	Contrast	F	p
	Diphenhydramine - Placebo	5.87	.0338
Drug	Diphenhydramine - Terfenadine	11.38	.0062
	Placebo - Terfenadine	ns	

Table 14.

Eyes main effect absolute power for EEG: Cz

	Eyes-opened	Eyes-Closed
Theta	19.60	26.35
Alpha	18.24	28.34
Beta	5.21	7.08

Table 15.

Contrasts for drug effect for EEG: Pz, alpha and beta

	Contrast	F	p
Alpha	Diphenhydramine – Placebo	5.48	.0391
	Diphenhydramine – Terfenadine	17.99	.0014
	Placebo – Terfenadine	ns	
Beta	Diphenhydramine – Placebo	6.98	.0229
	Diphenhydramine – Terfenadine	11.22	.0065
	Placebo – Terfenadine	ns	

Table 16.

Eyes main effect absolute power for EEG: Pz

	Eyes-opened	Eyes-closed
Theta	13.78	20.56
Alpha	22.19	36.63
Beta	4.39	5.71

Table 17.

Contrasts for drug effect for EEG: Oz, alpha and beta

	Contrast	F	p
Alpha	Diphenhydramine – Placebo	5.41	.0401
	Diphenhydramine – Terfenadine	10.84	.0072
	Placebo – Terfenadine	ns	
Beta	Diphenhydramine – Placebo	ns	
	Diphenhydramine – Terfenadine	8.52	.0140
	Placebo – Terfenadine	ns	

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Table 18.

Eyes main effect absolute power for EEG: Oz

	Eyes-opened	Eyes-Closed
Theta	8.39	14.55
Alpha	16.55	30.61
Beta	2.76	3.53

Appendix B

Illustrations
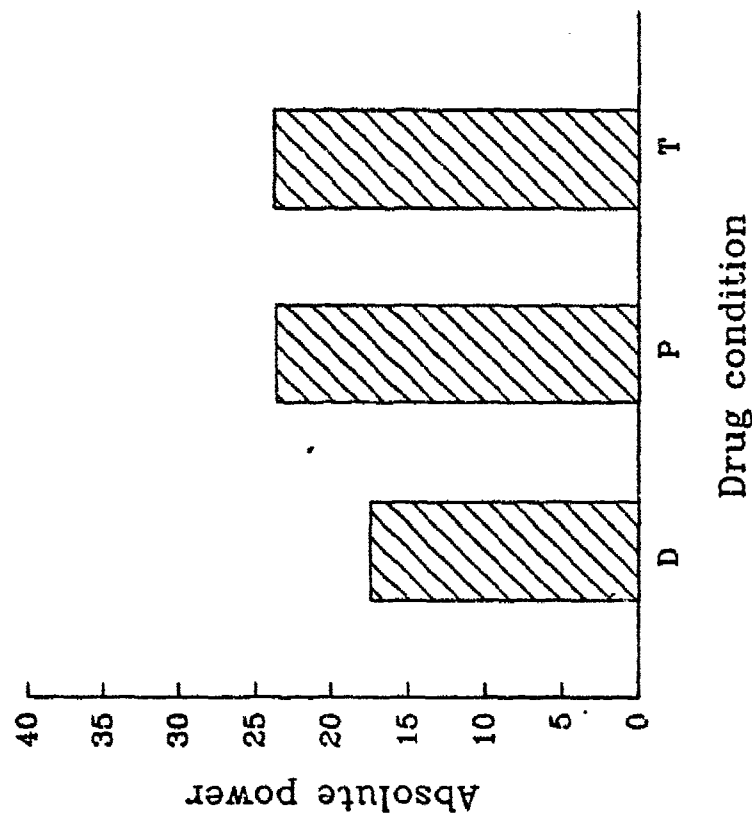
Figure 1. Drug main effect for resting EEG: Fz—alpha activity (D=diphenhydramine, P=placebo, T=terfenadine).

Fz – Beta activity

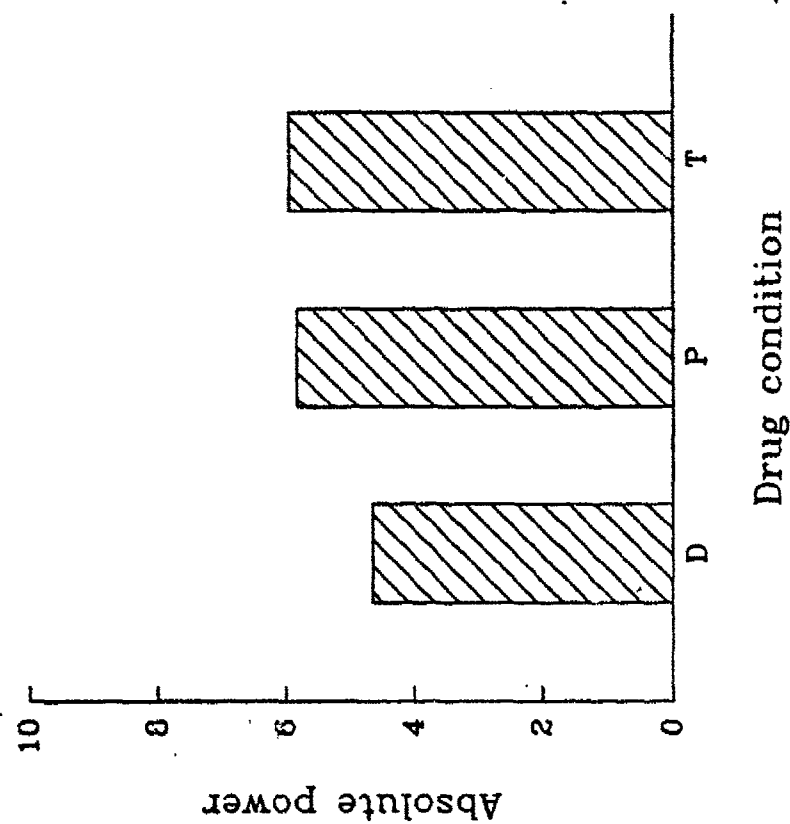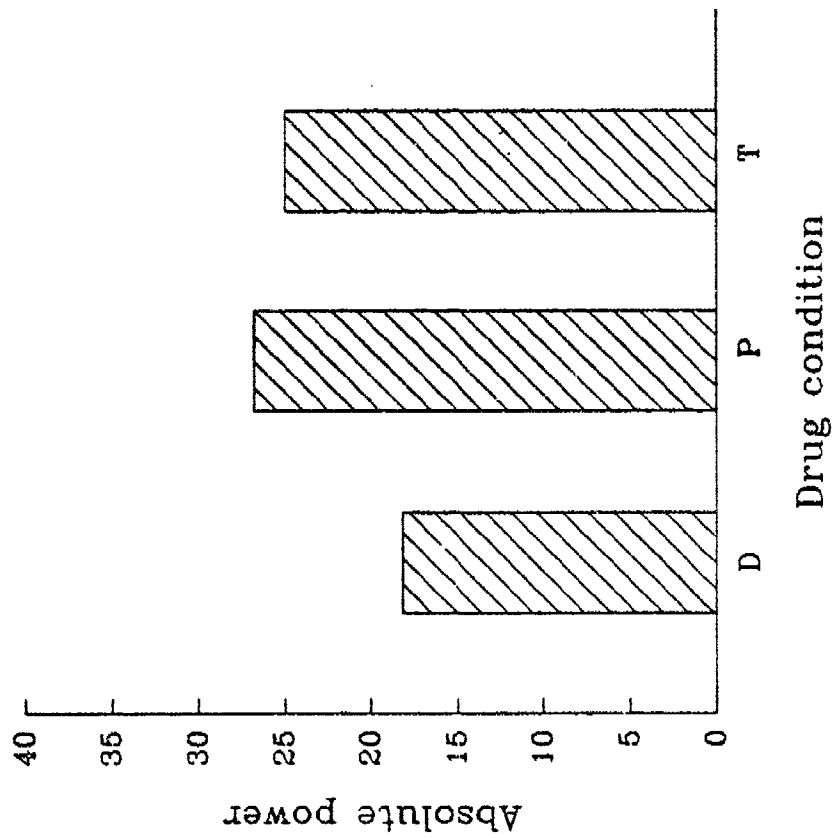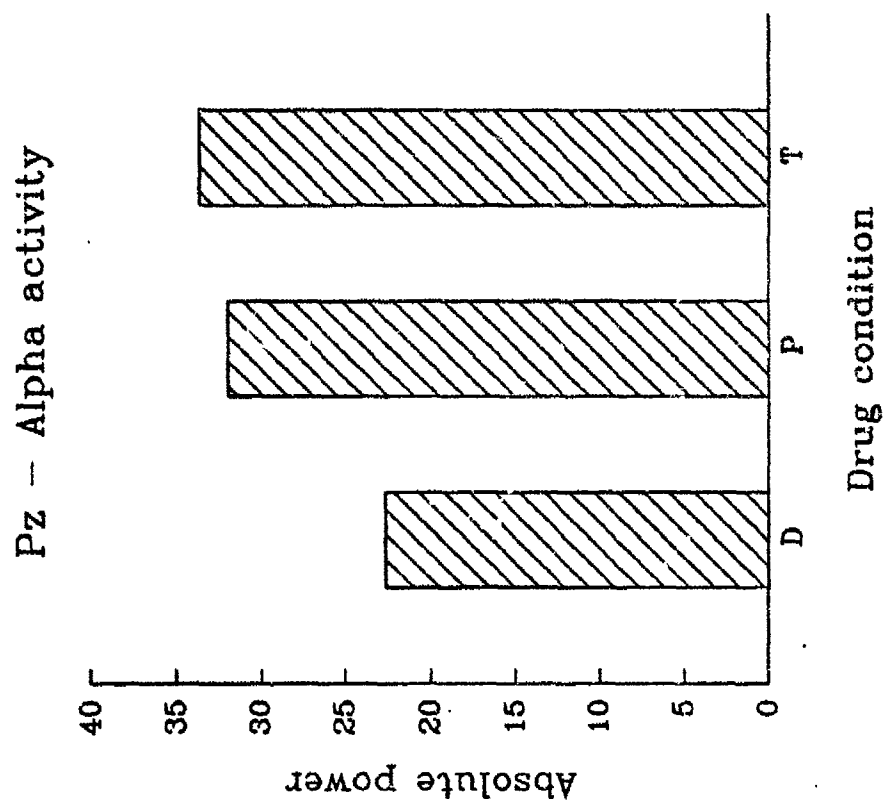Figure 2. Drug main effect for resting EEG: Fz—beta activity (D=diphenhydramine, P=placebo, T=terfenadine).
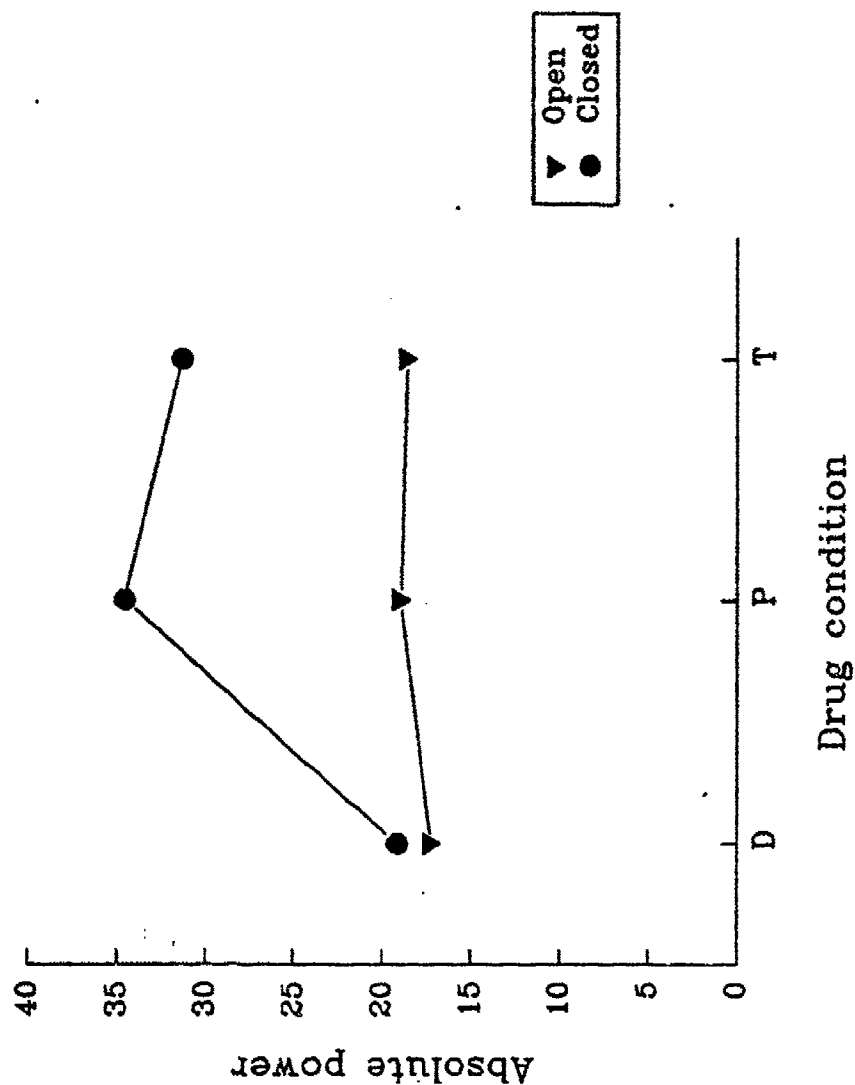
Figure 3. Drug x eyes interaction for resting EEG: Cz--alpha activity (D=diphenhydramine, P=placebo, T=terfenadine).

EYES OPENED

EYES CLOSED
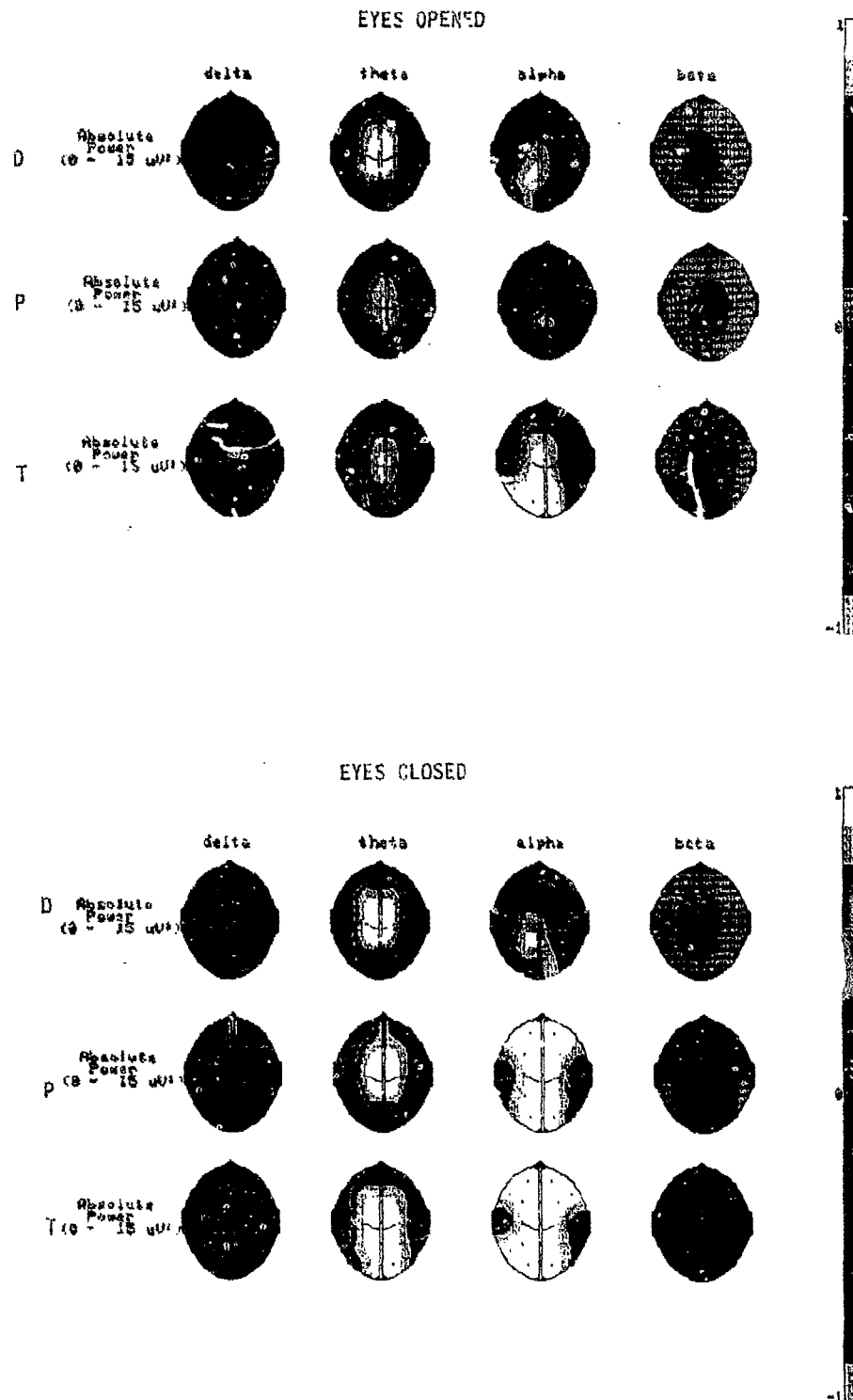
Figure 4. Topographical maps for resting EEG: Cz--alpha activity.

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Figure 5. Drug main effect for resting EEG: **Cz—alpha activity** (D=diphenhydramine, P=placebo, T=terfenadine).

Figure 6. Drug main effect for resting EEG: Pz--alpha activity
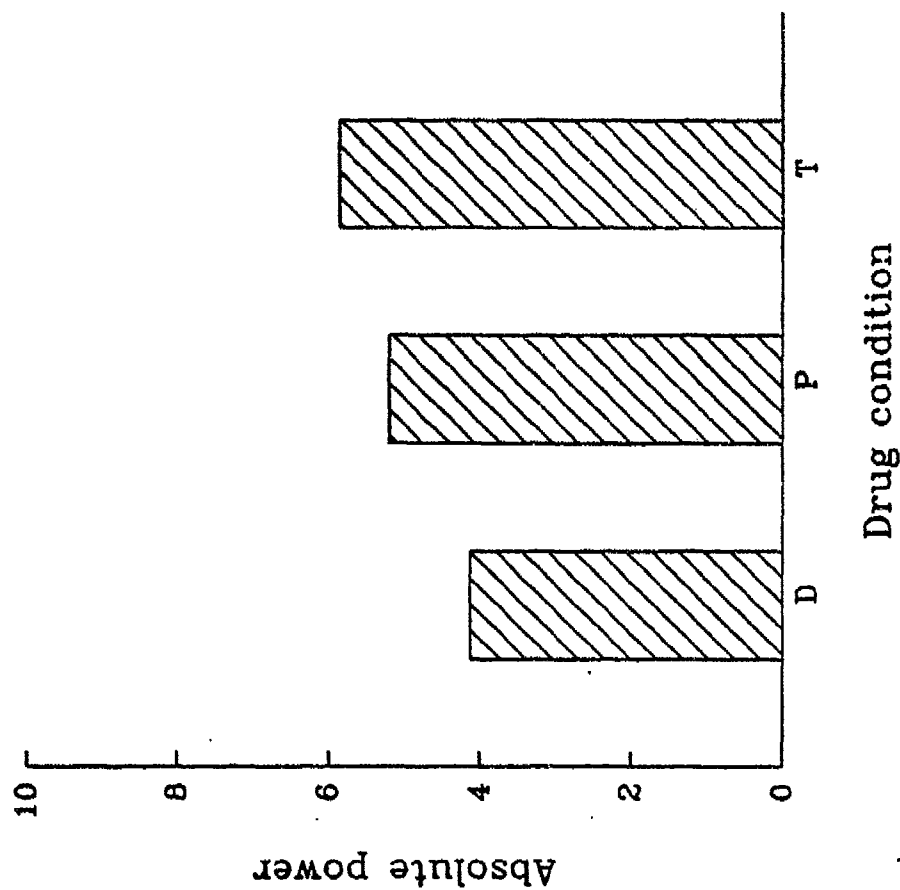(D=diphenhydramine, P=placebo, T=terfenadine).

Pz – Beta activity

Absolute power

Drug condition

Figure 7. Drug main effect for resting EEG: Pz--beta activity
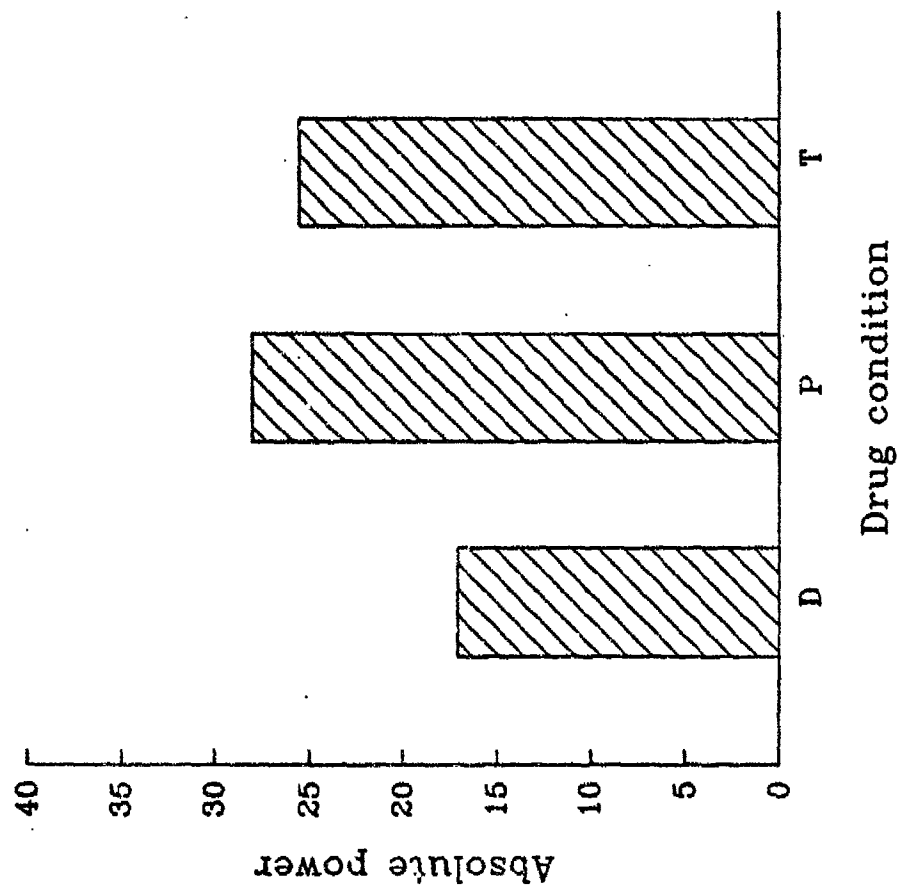(D=diphenhydramine, P=placebo, T=terfenadine).

Figure 8. Drug main effect for resting EEG: Oz--alpha activity (D=diphenhydramine, P=placebo, T=terfenadine).
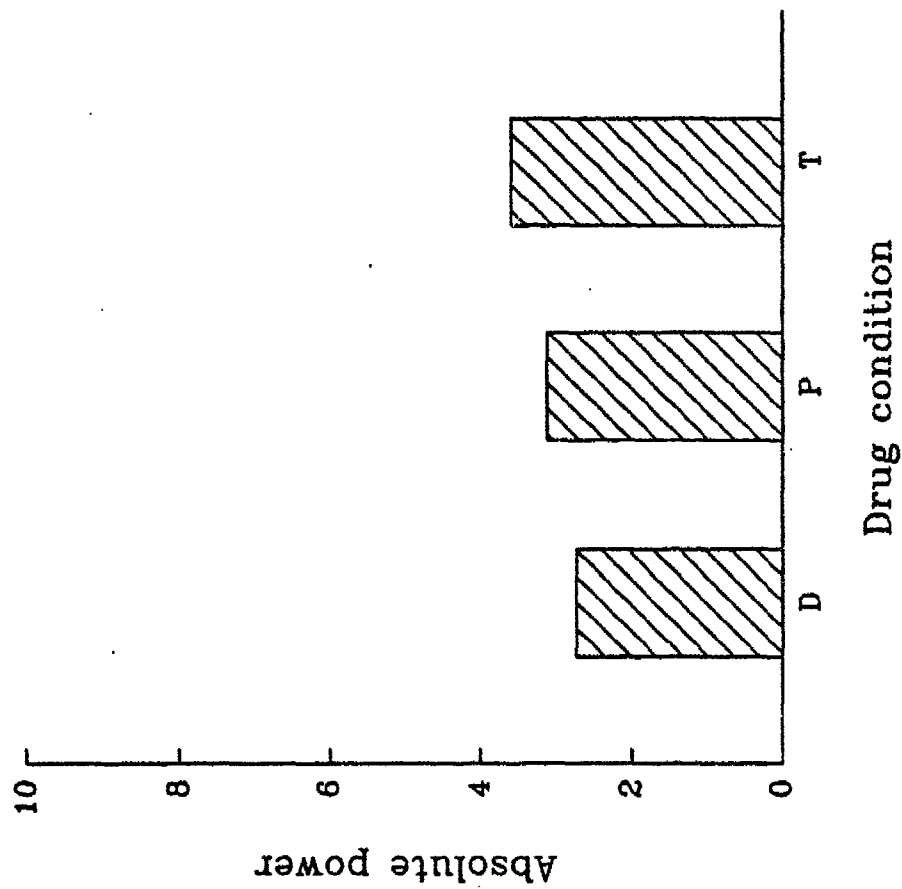
Oz — Beta activity

Figure 9. Drug main effect for resting EEG: Oz--beta activity
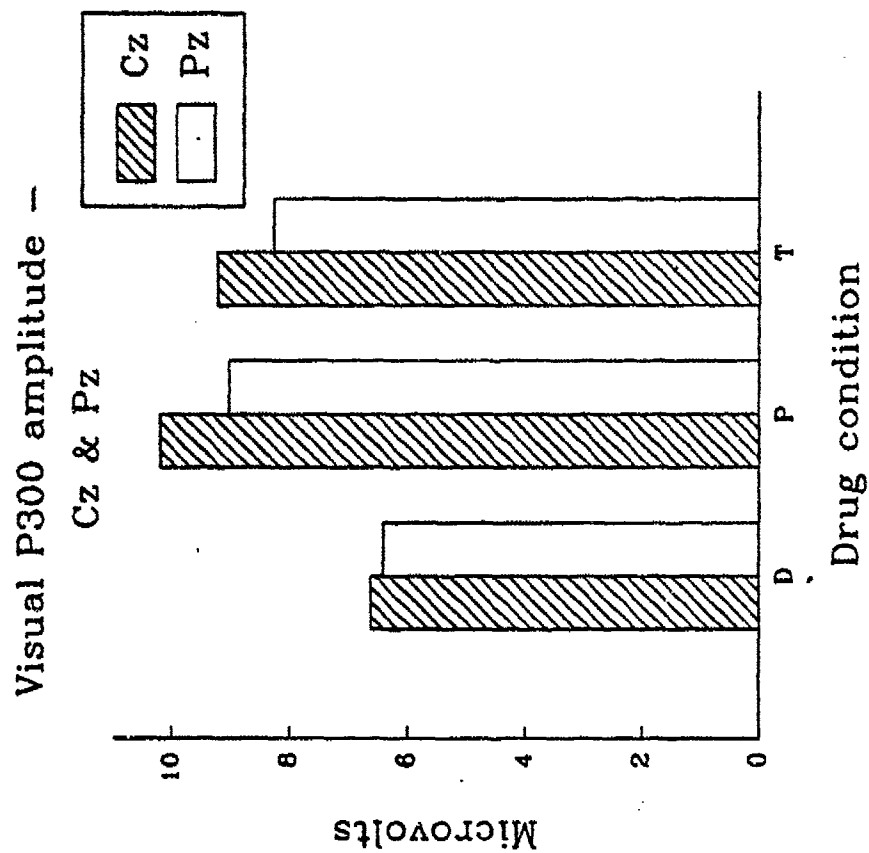(D=diphenhydramine, P=placebo, T=terfenadine).

Figure 10. Drug main effect for the visual evoked potential: Cz and Pz--amplitude of P300 (D=diphenhydramine, P=placebo, T=terfenadine).

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